INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/79188 A1

(51) International Patent Classification⁷: C07D 295/10, 295/08, 211/22, 471/04, 211/52, 473/08, A61K 31/495, 31/551, A61P 37/08 // (C07D 471/04, 239:00, 221:00)

(21) International Application Number: PCT/GB01/01748

(22) International Filing Date: 17 April 2001 (17.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0009479.7 17 April 2000 (17.04.2000) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

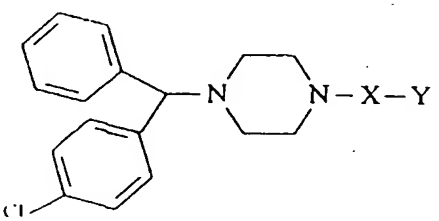
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
- *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/79188 A1

(54) Title: ANTIHISTAMINIC COMPOUNDS

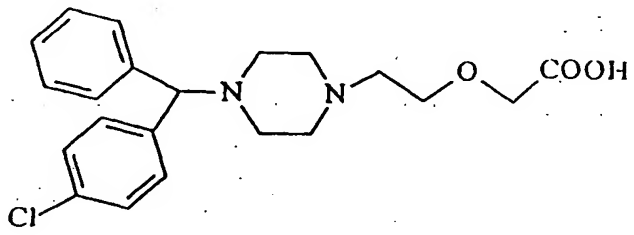


(I)

(57) Abstract: Antihistaminic compounds of formula (I) wherein X is an aliphatic hydrocarbonylene linker of preferably C_1-C_{10}, such as ethylene or carboxyethylene, wherein the only bond rotation in the linker is provided by an ethylene radical and X is preferably ethylene or carboxyethylene; and Y is a carbocyclic group, a heterocyclic group, a carbocyclic arenyl, a heterocyclic arenyl group, a polycyclic hydrocarbonyl, a heteropolycyclic group or theorbyline, and wherein Y can be optionally substituted as defined.

ANTIHISTAMINIC COMPOUNDS

The present invention relates to antihistaminic compounds, and more particularly to derivatives of the antihistaminic compound cetirizine (II) ([2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid)

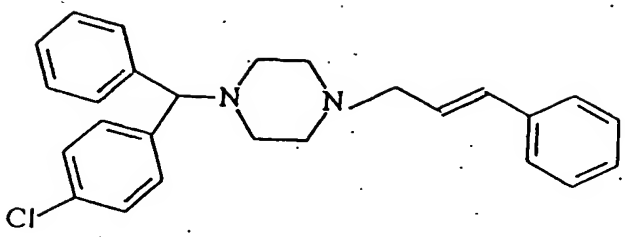


(II)

Cetirizine is an antihistamine and is typically delivered in an orally acceptable dosage form. Its principal effects are mediated via selective inhibition of peripheral H_1 receptors. Cetirizine is indicated for relief of symptoms associated with seasonal allergic rhinitis, perennial allergic rhinitis and for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria.

Whilst cetirizine is a useful agent for treating these indications, it suffers from a number of side-effects, the most common of which is drowsiness. Less common, but significant, side-effects include fatigue, dry mouth, dizziness, headache and nausea. The most likely reason why cetirizine induces drowsiness is that it can cross the blood-brain barrier. However, derivatives of cetirizine which incorporate more hydrophobic groups to block blood-brain barrier transport can lead to an unacceptable loss in antihistaminic potency.

For example, the antihistamine clocinizine (III) (1-[(4-chlorophenyl)phenylmethyl]-4-(3-phenyl-2-propenyl)piperazine), shares the

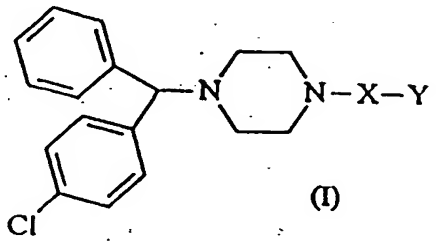


(III)

(4-chlorophenyl)phenylmethyl piperazinyl part with cetirizine, but instead of the more hydrophilic carboxyl group it has a more hydrophobic phenyl group. However, clocinizine is markedly less active than cetirizine.

We have now found that it is possible to provide compounds which are more active antihistamines than cetirizine, but which are also more hydrophobic.

According to one aspect, the present invention provides an antihistaminic compound of formula (I)



(I)

wherein:

X is an aliphatic hydrocarbonylene linker; Y is a carbocyclic group, a heterocyclic group, a polycyclic hydrocarbonyl group, a heteropolycyclic group, a carbocyclic arenyl group, a heteropolycyclic arenyl group, or theophylline; and

Y is optionally substituted with at least one substituent, the or each substituent being chosen from linear or branched C_1-C_{20} alkyl optionally substituted with one or more carbocyclic or heterocyclic groups, or a

substituent defined herein up to C_{20} cycloalkyl optionally including one or more heteroatoms from O, N and S, up to C_{20} bicycloalkyl optionally including one or more heteroatoms from O, N and S, up to C_{20} polycycloalkyl optionally including one or more heteroatoms from O, N and S, linear or branched C_1-C_{10} haloalkyl, linear or branched C_1-C_{10} perhaloalkyl, linear or branched C_2-C_{10} perhaloalkenyl, linear or branched C_2-C_{10} alkenyl, linear or branched C_2-C_{10} alkynyl, linear or branched C_1-C_{10} alkoxy, linear or branched C_1-C_{10} alkylthio, linear or branched C_1-C_{10} alkoxy (linear or branched C_1-C_{10} alkyl), linear or branched C_1-C_{20} alkoxycarbonyl, linear or branched C_1-C_{10} hydroxyalkyl, linear or branched aminoalkyl, aryl, substituted aryl, naphthyl, substituted naphthyl phenyl, heteroaryl, halogen, nitrile, nitro, amino, linear or branched C_1-C_{10} alkyl amino, linear or branched C_1-C_{10} dialkyl amino linear or branched C_1-C_{20} alkoxycarbonyl, hydroxyl, formyl acetyl, carboxyl, carbonyl, amido, C_1-C_5 alkyl amido C_1-C_5 dialkylamido, aroyl, benzoyl, arylamino, diarylamino, aryl C_1-C_{10} alkyl amino, aziridino, pyrrolidino, piperidino, morpholino, thiomorpholino, indolino, piperazino, C_1-C_5 N-alkyl piperazino or N-aryl piperazino; and each cyclic substituent can in turn be substituted by one or more substituents as defined herein characterised in that the only bond rotation in the X linker is provided by an ethylene radical.

Preferably the X linker is a C_2 - C_{10} aliphatic hydrocarbonyl linker such as C_3, C_5 or C_8, but it is preferably an ethylene or carboxyethylene radical.

Without wishing to be bound by theory, we believe that the X linker between the piperazinyl part and the Y part requires a flexible carbon-carbon bond wherein the bond between each carbon atom and from each carbon atom is freely rotatable. We further believe that this flexibility feature aids the interaction of the compounds according to the invention with the H_1-receptor.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

According to a further aspect, the present invention provides a compound of the invention for use as a medicament.

The present invention also provides the use of a compound of the present invention in the manufacture of a medicament for the treatment of antihistaminic conditions.

According to a further aspect of the present invention, there is provided the use of 4-chlorobenzhydrylpiperazine ethylchloride to make a compound according to the present invention..

According to a further aspect of the present invention, there is provided the use of 4-chlorobenzhydrylpiperazine to make a compound according to the present invention.

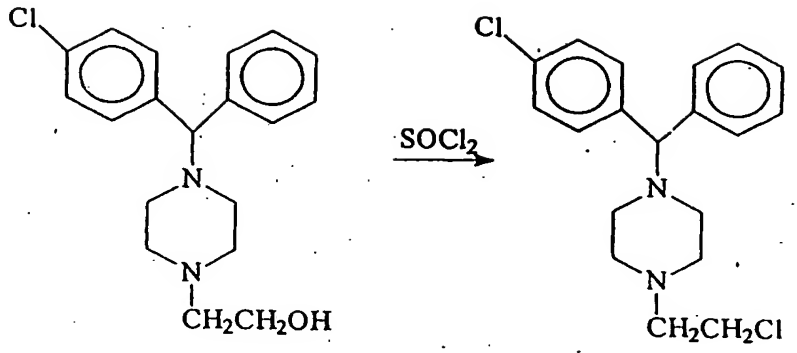
The compounds of the present invention can be formulated for administration to a patient in any convenient manner, for example for oral or parenteral routes of administration. We presently prefer an oral dosage tablet wherein a core containing the active ingredient is coated with an enteric coating. However, the composition may also be provided as a flavoured syrup to mask any unpleasant taste. An injectable formulation is one embodiment of a composition suitable for parenteral administration.

In order that the invention may be more fully understood, reference will be made to the following Examples, by way of illustration only.

Example 1

Synthesis of 4-chlorobenzhydrylpiperazine ethylchloride.

4-chlorobenzlhydrylpiperazine ethylchloride is an intermediate for making many of the compounds of the present invention.



20g (0.04944 moles) of 4-chlorobenzhydrylpiperazine ethanol dihydrochloride was dissolved in a 100ml methanol in a 250ml three necked round bottom flask under stirring. To the clear solution 4g (0.1 moles) of sodium hydroxide was added and mixture was stirred for 30 minutes. Sodium chloride obtained was filtered and distilled off methanol completely. Chloroform (100ml) was added to the same flask stirred for 15 minutes. To the clear solution 40ml thionyl chloride was added and reaction mixture was refluxed for 5-6 hrs. Solid precipitated out was filtered.

The filtered solid was transferred to a 500ml round bottom flask containing 200ml acetonitrile and 5.2g (0.5 moles) of sodium carbonate, the mixture was stirred. The reaction mixture was refluxed for 2 hrs and filtered. Acetonitrile was distilled out under reduced pressure to obtain free base.

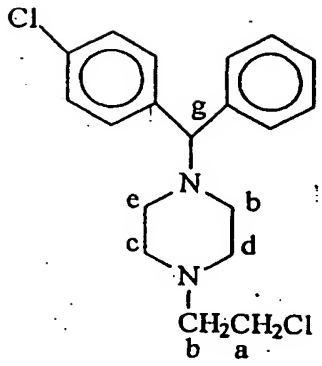
Yield : 15.53g (90%)

M.P. : 196-198°C

TLC : Mobile phase : Benzene : MeOH (10:1) Rf: 0.8

Spectral Characteristics:

^{1}H NMR ($CDCl_3$)



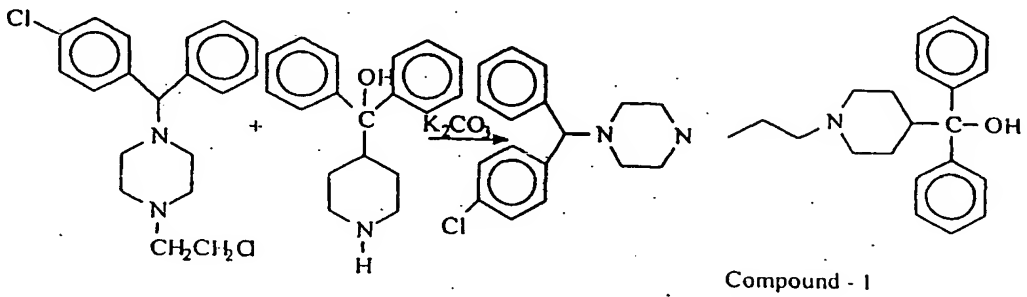
Chemical shift δ	Multiplicity	Intensity	Protons
2.5-3	m	10H	c,d,e,f
3.7-3.9	t	2H	a
4.2	s	1H	g
7-7.5	m	9H	aromatic

IR(KBr) cm^{-1}

presence of -OH peak.

Example 2

Synthesis of 1(4-chlorobenzhydryl)-4-ethyl-[2'[4"-(2-hydroxy-benzhydryl]piperidine]piperazine



Compound - I

2g (0.005730 moles) of 4-chlorobenzhydryl piperazine ethyl chloride was introduced into a 100ml three necked bottom flask containing 30ml dry DMF, 0.8292g (0.006 moles) of anhydrous potassium carbonate and 0.002g of

potassium iodide. The reaction mixture was stirred for 30 minutes. To the same flask 1.52g (0.005730 moles) of azacyclonol was added. The reaction mixture was heated to 100°C for 16 hrs and then allowed to cool to 30°C. A solid separated out by quenching reaction mixture in a ice under stirring. The solid product so obtained was filtered and dried in oven at 60°C for 4 hrs.

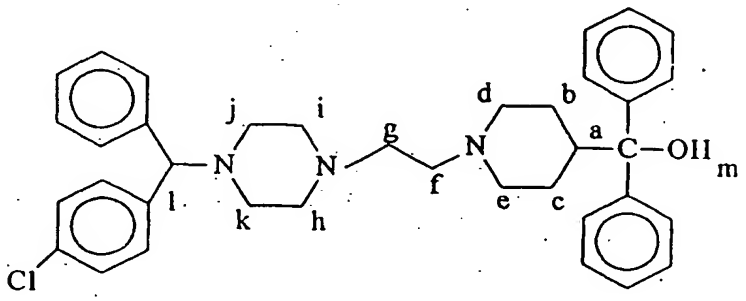
Yield : 2.8g (84.31%)

M.P. : 130-134°C

TLC : Mobile Phase : Et.Ac : Benzene : Ammonia (5 : 2 : 0.2) Rf : 0.6

Spectral characteristics:

^{1}H NMR ($CDCl_3$)



Chemical shift δ	Multiplicity	Intensity	dProtons
1.4-1.8	m	5H	a,b,c
2.2-3	m	16H	d,e,f,g,h,i,j,k
3.4	bs	1H	m (D_2O exchangeable)
4.3	s	1H	l
7.1-7.7	m	19H	aromatic

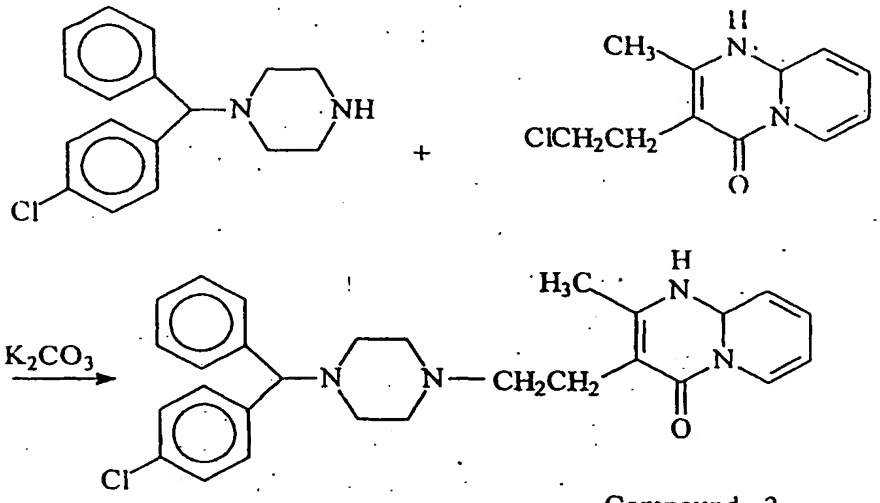
IR (KBr) cm^{-1}

3435.5 (-O-H)

2900-3000 (-C-H str.)

Example 3

Synthesis of 1-4-chlorobenzhydryl)-4-ethyl-2"[2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one] piperazine



Compound - 2

4G (0.01396) of 4-chlorobenzhydryl piperazine was dissolved in 30ml DMF in a three necked 100ml round bottom flask equipped with condensor and thermometer pocket. To the clear solution 1.939g (0.014) of potassium carbonate, 3.134g (0.01396) of pyridopyrimidinone and catalytic amount of potassium iodide was added under stirring. The reaction mixture was refluxed for 10 hrs and then cooled to 25-30°C under stirring. A solid was precipitated out by pouring the reaction mixture in ice-cold water. The solid material obtained was filtered and washed with water thoroughly. The product was dried in oven at 50°C for 4 hrs.

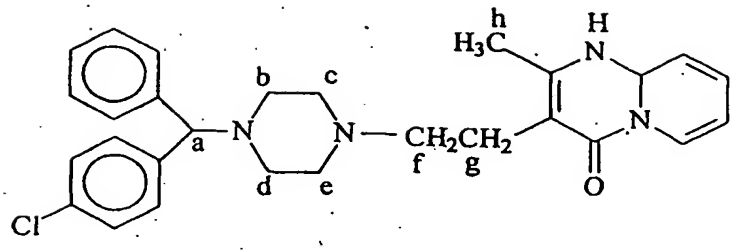
Yield : 4.63g (70%)

M.P. : 85-90°c

T.L.C : Mobile Phase : Benzene : Methanol (5 : 0.2) Rf : 0.5

Spectral characteristics

^{1}H NMR ($CDCl_3$)



Chemical shift δ	Multiplicity	Intensity	Protons
2.2	m	4H	b,d
2.5	s	3H	h
2.6-3.1	m	4H	c,e
3.2-3.6	m	4H	f,g
4.1	s	1H	a
7-7.5	m	13H	aromatic

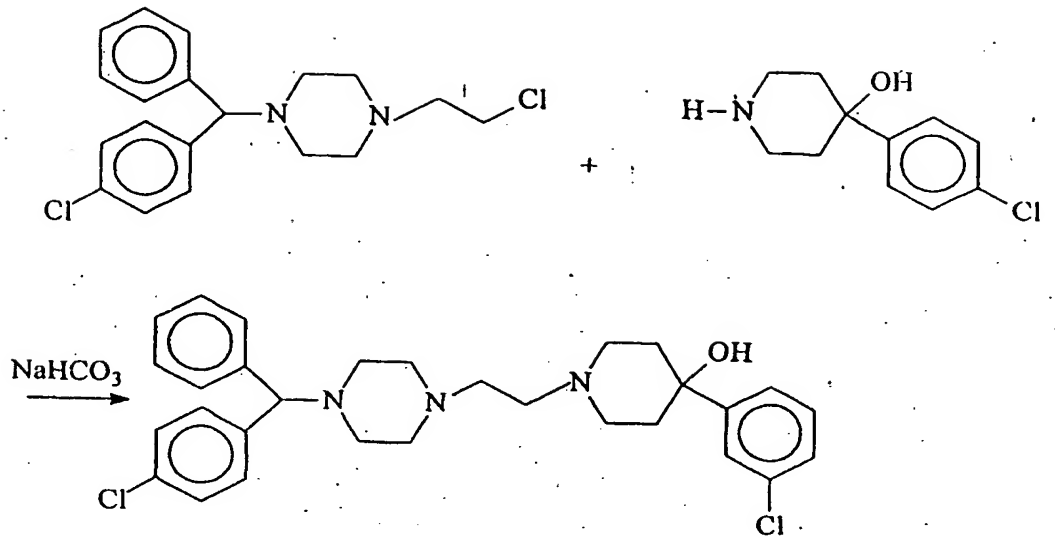
IR (KBr) cm^{-1}

1692 (C=O)

1098 (C-Cl str.)

Example 4

Synthesis of (4-chlorobenzhydryl)-4-ethyl-[2'[4"-(p-chlorophenyl)-4"-hydroxy]piperidine]piperazine



Compound - 3

2g (0.005730 moles) of 4-chlorobenzhydryl piperazine ethylchloride was introduced in to 100ml three necked round bottom flask containing 1.5g (0.0178 moles) of sodium bicarbonate, 15ml toluene and 0.002g of potassium iodide under stirring. Stirring was continued for 30 minutes. 1.3g (0.005730) of 4-hydroxy-4-(p-chlorophenyl)-piperidine was added and the mixture was refluxed for 16 hrs. The reaction mixture was cooled to 30°C and filtered. Toluene was distilled out completely under vacuum. Water was added to the residue under stirring. Solid precipitated-out was filtered and washed with water. The product was dried in oven at 50°C for 4 hrs.

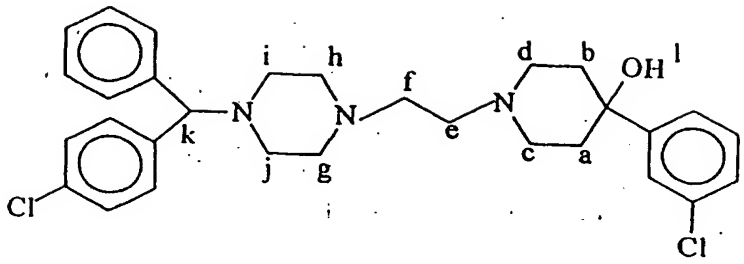
Yield : 2.40g (80%)

M.P. : 96-100°C

TLC : Mobile Phase : Chloroform : Methanol (9 : 1) Rf : 0.5

Spectral characteristics:

^{1}H NMR $CDCl_3$



Chemical shift δ	Multiplicity	Intensity	Protons
1.5-2	m	4H	a,b
2.2-3	m	16H	c,d,e,f,g,h,i,j
4	bs	1H	l
4.2-4.3	s	1H	k
7-7.6	m	13H	aromatic

IR (KBr) cm^{-1}

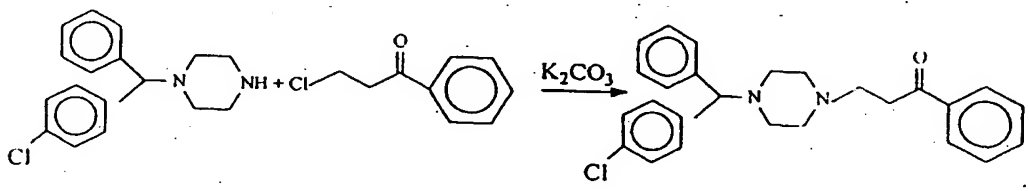
3407 (O-H)

2948 (C-H str.)

1089 (C-Cl str.)

Example 5

Synthesis of 1-(4-chlorobenzhydryl)-4-(3-phenyl-3-propanone)-piperazine



Compound - 4

2g (0.0068) of 4-chlorobenzhydryl piperazine was dissolved in 15ml toluene in a 50ml three necked round bottom flask equipped with thermometer pocket and condensor. To the clear solution 1.126g (0.0068) of 3-chloropropiophenone, 1.2g (0.0086) of potassium carbonate and catalytic amount of potassium iodide was added under stirring. The reaction mixture was refluxed for 4 hrs. and filtered to remove inorganic material. The toluene was distilled out under vacuum to obtain oily residue. The solid was separated out by addition of hexane to the oily material under stirring. The solid product was filtered and dried in oven at 50°C for 2 hrs.

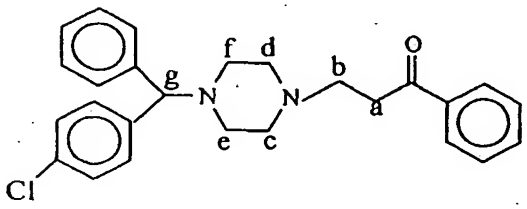
Yield : 2.45g (84%)

M.P. : 105-108°C

TLC : Mobile Phase : Benzene : MeOH (10 : 0.8) Rf : 0.42

Spectral characteristics:

^{1}H NMR ($CDCl_3$)



Chemical shift δ	Multiplicity	Intensity	Protons
2.1-2.8	m	12H	a,b,c,d,e,f
3.9-4.0	s	1H	g
6.7-7.2	m	14H	aromatic

IR (KBr) cm^{-1}

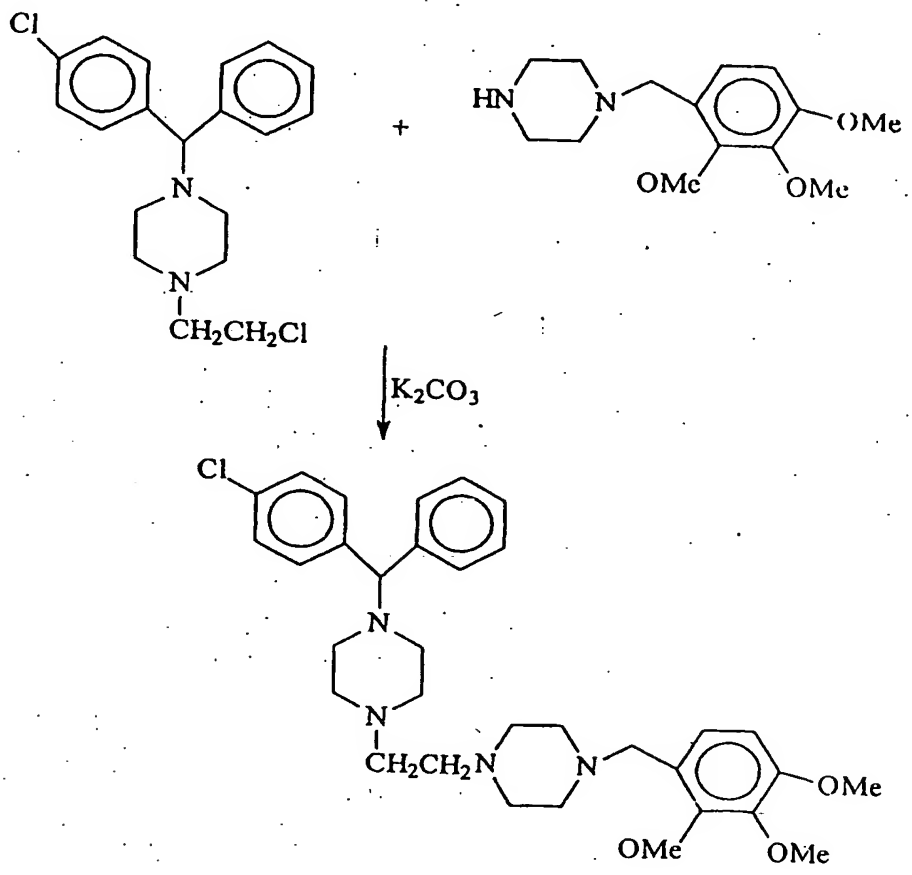
2913-3000 (C-H str.)

1681 (C=O)

1089 (C-Cl str.)

Example 6

Synthesis of 1-(4-chlorobenzhydryl)-piperazine-4-ethyl-2'[4"(2,3, 4-trimethoxy benzyl)]piperazine



Compound 5

2g (0.005770 moles) of 4-chlorobenzhydryl piperazine ethyl chloride and 1.9426g (0.005730 moles) of trimetazidine were added in a 100ml three necked round bottom flask containing 20ml dry DMF, 1.575g (0.0114 moles) of potassium carbonate and 0.001g of potassium iodide. The reaction mixture was heated to 100-110°C for 8 hrs and then allowed to cool to 30°C. It was

then added to a beaker containing ice water under stirring. The product was extracted with chloroform (2x1.5ml) and chloroform layer was washed with water. The washed chloroform layer was dried over an sodium sulfate and the chloroform was evaporated completely. Etheral hydrochloride was added to the residue and the pH was adjusted to 2 under stirring precipitating a solid. The solid was filtered and dried in a vacuum at 60°C.

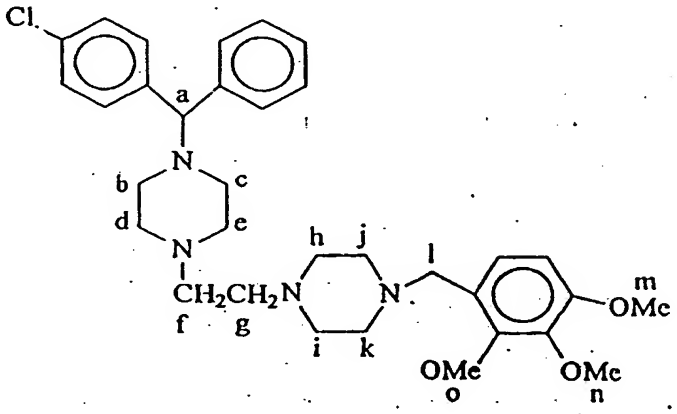
Yield : 2.8g (75%)

M.P. : 234-236°C

TLC : Mobile Phase : Ethyl acetate Rf : 0.42

Spectral characteristics:

^{1}H NMR ($DMSOd_6$)



Chemical shift δ	Multiplicity	Intensity	Protons
2.2-2.8	m	20H	b,c,d,e,f,g,h,i,j,k
3.9	s	9H	m,n,o
4-4.2	m	3H	a,l
7.1-7.3	m	11H	aromatic

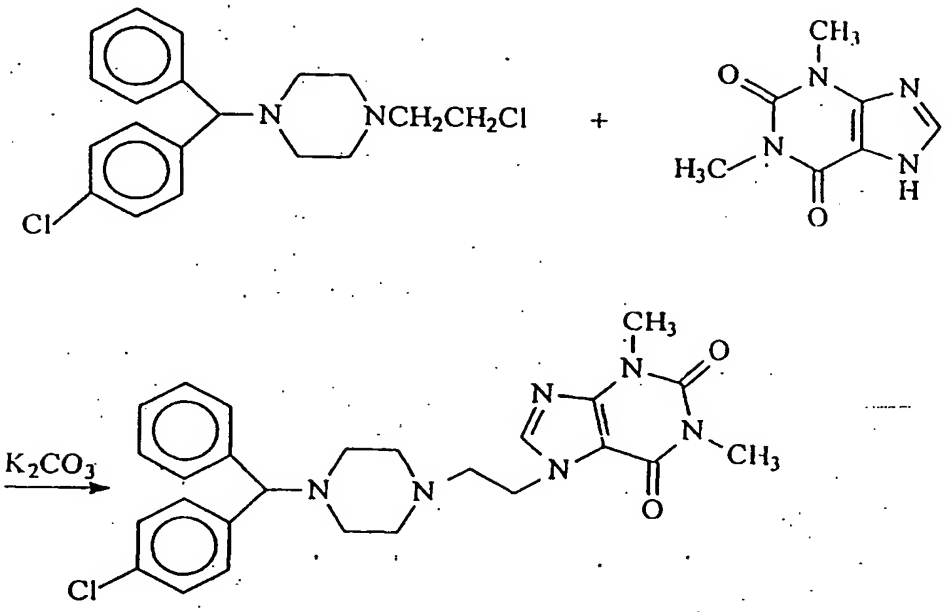
IR (KBr) cm^{-1}

2960-3000 (C-H str.)

1099 (C-O-C str.)

Example 7

Synthesis of 1-(p-chlorobenzhydryl)4-ethyl-2'-[1,3-dimethyl xanthine]-piperazine



Compound - 6

2g (0.0047 moles) of 4-chlorobenzhydryl piperazine ethylchloride dihydrochloride was added to a 100ml three necked bottom flask containing 30ml DMF, 2.7g (0.01950) moles of potassium carbonate and 0.001g of potassium iodide. The reaction mixture was stirred for 30 minutes. To the same flask 0.853g (0.0047 moles) of theophylline was added. The reaction mixture was heated to 100-110°C for 16 hrs and then allowed to cool to 30°C. A solid was precipitated by quenching the reaction mixture in icy water under stirring. The solid product obtained was filtered and dried in oven at 50°C for 4 hrs.

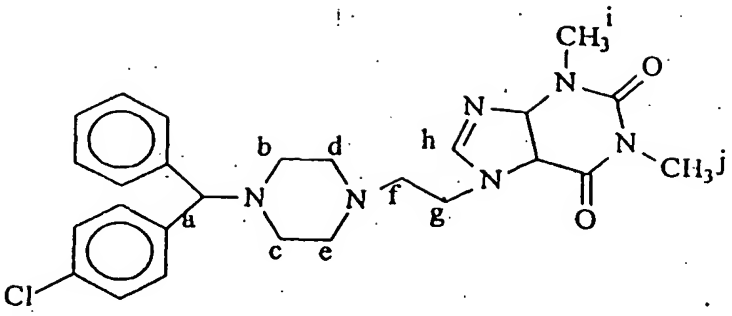
Yield : 2.03g (87%)

M.P. : 98-100°C

TLC : Mobile Phase : Ethyl acetate Rf : 0.5

Spectral characteristics:

^{1}H NMR (CCl^4)



^{1}H NMR CCl_4

Chemical shift δ	Multiplicity	Intensity	Protons
2.2-2.8	m	10H	b,c,d,e,f
3.3	s	3H	i
3.4	s	3H	j
4-4.2	m	3H	a,g
7-7.5	m	10H	aromatic,h

IR (KBr) cm^{-1}

2960 (C-H str.)

1653 (C=O str.)

Example 8

Biological Activity Testing

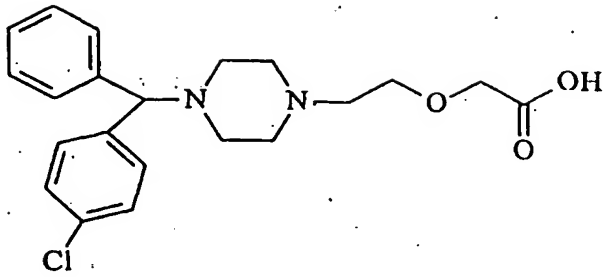
Antihistaminics are evaluated in vitro by Magnus procedure (see Ghosh, M N and Schild, H O, *Fundamentals of Experimental Pharmacology*, 63, 1971; Schmidt, L and Seeger E, *Arzneim. Forsch (Drug Research)*, 6, 22, 1956) in which the minimum amount of drug is measured which relaxes histamine-induced spasm in an isolated strip of guinea pig's small intestine

immersed in Tyrode solution. The isolated ileum of guinea pig is the most sensitive and accurate test object for the assay of histamine. A piece of terminal ileum was suspended in an isolated bath in Tyrode solution containing 0.6mg/ml atropine sulphate. This eliminates or reduces contractile responses due to cholinergic agents, causes relaxation of the guinea pig ileum producing a fixed base line and reduces or eliminates spontaneous contractile activity in the guinea pig ileum. The bath was kept at 35°C, and kept oxygenated with a continuous supply of oxygen or air. A frontal writing lever magnified 10 times and with tension of 1g was used for recording the contractions.

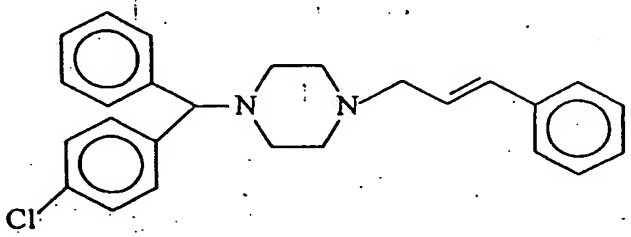
Contraction of the guinea pig ileum to histamine was observed for 30 seconds; relaxation during rinsing or washing of the bath with 2 or 3 changes of Tyrode solution was also almost complete in 1.5 minutes. Hence contractions for exactly 30 seconds were regularly obtained at intervals of 1.5 minutes. The tissue preparation gave good response to histamine in various concentration range (1μg-100μg). The results were analysed using the 'Latin Square' technique to provide a standard curve of histamine response, and the mean contraction of the responses for each dose of histamine was calculated. For quantitative estimation of IC_{50} value of the synthesized compounds, the one single standard dose of histamine was repeated until the fixed standard length of contraction of histamine response was obtained. The mean length of contraction of standard histamine was evaluated as the 100% std. response, and this was used to determine the IC_{50} and IC_{100} for the antihistamine (antagonist) to be tested. Antagonists were added to the Tyrode solution simultaneously with the standard dose of histamine and the contraction response was determined. The tissue was washed with fresh Tyrode solution before addition of a different antagonist concentration.

Comparative compounds

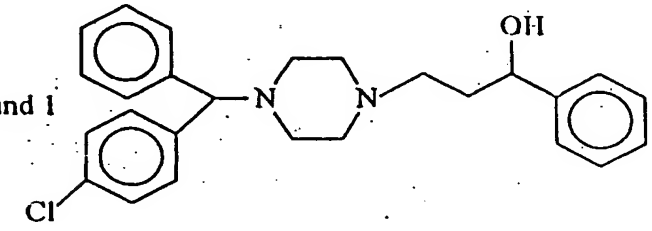
Cetirizine



Clocinizine

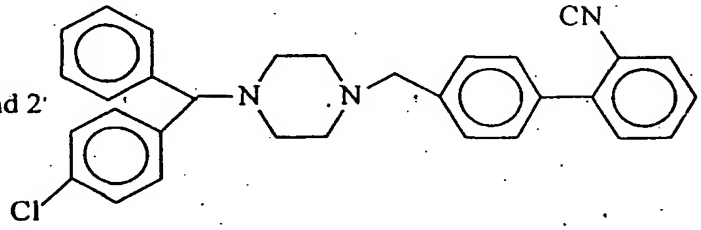


Comparative compound 1



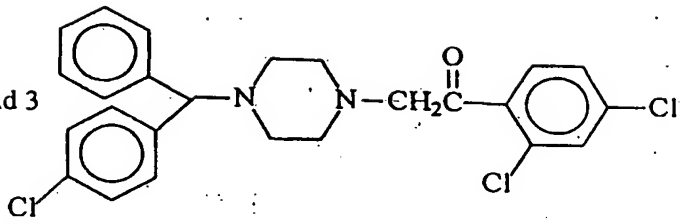
1-(4-chlorobenzhydryl)-4-(3-phenyl-3-propanol)-piperazine

Comparative compound 2



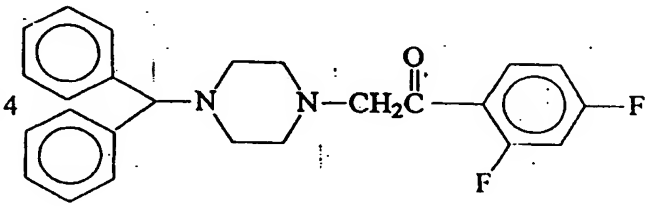
1-(4-chlorobenzhydryl)-4-methyl(2-cyanobiphenyl)-piperazine

Comparative compound 3



1-(4-chlorobenzhydryl)-4-(2(2',4'-dichlorobenzene)ethan-z-one

Comparative compound 4



1-(4-chlorobenzhydryl)-4-(2(2',4'-difluorobenzene)ethan-2-one)piperazine

The results of the Magnus procedure experiment for each of compounds 1 to 6 and the comparative compounds 1 to 6 and the comparative compounds cetirizine, clocinizine and comparative compounds 1 to 4 are shown in Table 1 below.

Table 1:
Results of Magnus procedure experiments

Comp No.	Dose µg	% inhibition	molar conc. [c]	Log [c]	ED50 µg / ml	PA_2 = $-\log ED_{50}$	log P
1	0.5	6.25%	8.6281×10^{-7}	-6.06408			
	1	12.5%	1.7256×10^{-6}	-5.7630	2.0561	5.45	7.658
	2	31.25%	3.4513×10^{-6}	-5.4620			
	4	100%	6.9025×10^{-6}	-5.1609			
2	1	0.0%	2.1075×10^{-6}	-5.6762			
	2	37.5%	4.2150×10^{-6}	-5.3752			
	4	62.5%	8.4300×10^{-6}	-5.0741	2.6608	5.25	5.083
	8	75.0%	1.6860×10^{-5}	-4.7731			
	10	100%	2.1075×10^{-5}	-4.6762			
3	0.11	6.0%	2.0985×10^{-7}	-6.6780			
	0.22	9.0%	4.1970×10^{-7}	-6.3770			
	0.44	15.1%	8.3940×19^{-7}	-6.0760			
	0.88	15.1%	1.6788×10^{-6}	-5.7750			
	1.1	21.2%	2.0984×10^{-6}	-5.6781			
	2.2	24.2%	4.1970×10^{-6}	-5.3770	11.7351	4.65	6.524
	4.4	27.2%	8.3940×10^{-6}	-5.0760			
	6.6	30.3%	1.2591×10^{-5}	-4.8999			
	8.8	39.3%	1.6788×10^{-5}	-4.7750			
	11.0	48.4%	2.0985×10^{-5}	-4.6780			
	16.5	60.6%	3.1477×10^{-5}	-4.5020			
	22	87.8%	4.1970×10^{-5}	-4.3770			
	27.5	96.96%	5.2462×10^{-5}	-4.2801			
	28	100%	5.3416×10^{-5}	-4.2723			
4	10	30%	2.0346×10^{-5}	-4.6915			
	20	50%	4.0692×10^{-5}	-4.3904			
	30	70%	6.1037×10^{-5}	-4.2144	19.566	4.4	6.318

	35	90%	7.1210×10^{-5}	-4.1474			
	37.5	100%	7.6298×10^{-5}	-4.1174			
5	10	4%	1.5349×10^{-5}	-4.8139			
	20	4%	3.0698×10^{-5}	-4.5129			
	40	20%	6.1397×10^{-5}	-4.2153	46.1226	4.15	6.15
	50	92%	7.6746×10^{-5}	-4.1873			
	55	100%	8.4420×10^{-5}	-4.1483			
6	10	14.2%	2.0304×10^{-5}	-4.6924			
	20	43.0%	4.0609×10^{-5}	-4.3913			
	30	72.0%	6.0913×10^{-5}	-4.2153	21.9999	4.35	4.418
	32	86.0%	6.4975×10^{-5}	-4.1873			
	35	100%	7.1066×10^{-5}	-4.1483			
Std.	10	0.0%	2.16×10^{-5}	-4.6655			
Cetirizine	20	22.85%	4.33×10^{-5}	-4.3635			
	30	84.28%	6.50×10^{-5}	-4.1870			
	35	85.7%	7.58×10^{-5}	-4.1203			
	40	92.85%	8.66×10^{-5}	-4.0624	25.95	4.25	2.221
	50	95.71%	1.083×10^{-4}	-3.9653			
	60	97.14%	1.3×10^{-4}	-3.8860			
	70	98.57%	1.51×10^{-4}	-3.8210			
	75	100%	1.62×10^{-4}	-3.7904			
Std.	20	10.52%	4.0527×10^{-5}	-4.3923			
Clocinizine	40	15.7%	8.1054×10^{-5}	-4.0912			
	80	15.7%	1.6211×10^{-4}	-3.7902			
	160	21.0%	3.242×10^{-4}	-3.4892			
	200	26.3%	4.0527×10^{-4}	-3.3923	439.8323	3.05	6.851
	300	31.5%	6.0790×10^{-4}	-3.2162			
	400	42.1%	8.1053×10^{-4}	-3.0912			
	500	63.15%	1.01317×10^{-3}	-2.9943			
	600	78.9%	1.2158×10^{-3}	-2.9151			
	700	84.2%	1.4184×10^{-3}	-2.8482			
	800	94.7%	1.6211×10^{-3}	-2.7901			

	840	100%	1.7021×10^{-3}	-2.7690			
Comparative Compound 1	10	0%	2.0263×10^{-5}	-4.6933			
	20	18.42%	4.0526×10^{-5}	-4.3922	31.1377	4.2	5.398
	40	57.89%	8.1033×10^{-5}	-4.0912			
	50	100%	1.0137×10^{-4}	-3.9943			
Comparative Compound 2	3μg of histamine was not inhibited by even 250μg of comparative compound 2						7.862
Comparative Compound 3	40μg of histamine was not inhibited by even 500μg of comparative compound 3						7.22
Comparative Compound 4	40μg of histamine was not inhibited by even 500μg of comparative compound 4						6.468

In the above table, the % inhibition values were determined from kaymograph. The log[C] vs % inhibition was plotted to get ED_{50} values for the compounds 1-11. Further, $-\log ED_{50}$ was calculated to obtain PA_2 values.

As will be seen by comparing the ED50 and PA_2 (log ED50) values, compounds 1 to 4 are potent H_1-receptor antagonist by reference to the known antihistamine cetirizine and clocinizine, whilst compounds 5 and 6 show a moderate, but significant, increase in potency. Comparative compound 1 has a similar activity to cetirizine, but it is more lipophilic.

The calculated LogP of the synthesized and tested compounds between 5-7.7 was found optimum for good H_1-receptor antagonist activity. Hence logP, a parameter for lipophilicity, shows that lipophilicity has an important role for eliciting the biological response of these compounds. LogP by its nature governs the pharmacokinetic profile of the compounds. The more lipophilic a compound the less likely it is to cross the blood-brain barrier. Compounds 1 to 6 and comparative compound 1 are therefore less likely to cause drowsiness.

Furthermore, a comparison of the activity of clocinizine and comparative compound 1 with compounds 1 to 6 shows that an important feature of the present invention is that the linker X in formula (I) should be ethylene or a radical including a carbon-carbon bond which is free to rotate. A substituted propylene radical X linker (compare compound 4 and comparative compound 1) including two freely rotatable carbon-carbon bonds results in a less antihistaminically active molecule.

Example 9

Oral dosage tablet containing 10mg of 1-(4-chlorobenzhydryl)-4-ethyl-[2'[4"-(2-hydroxybenzhydryl]piperidine] piperazine (compound 1)-hydrochloride.

Each film coated tablet contains Compound 1 hydrochloride.....10mg

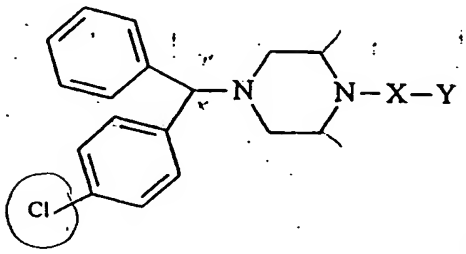
INGREDIENTS	QTY/TAB (mg)
Compound 1 hydrochloride	10.0
Lactose IP	80.0
Starch IP	25.20
Magnesium stearate IP	2.0
Colloidal Silicon dioxide IP	1.0
Talc IP	1.8
	120.0

The above formulation includes standard fillers and glidants well known to those of skill in the art. The skilled person will be able to scale-up production to batch size using the above amounts as a guide or with routine experimentation. The processes for dry mixing of the ingredients for tablet compression or for encapsulation into capsules are also well known and will not be discussed further herein.

Tablets so formed may be coated with suitable water soluble or water insoluble polymers or polymers which have pH dependent solubility, as desired.

CLAIMS:

1. An antihistaminic compound of formula (I)



(I)

wherein:

X is an aliphatic hydrocarbonylene linker; Y is a carbocyclic group, a heterocyclic group, a polycyclic hydrocarbonyl group, a heteropolycyclic group, a carbocyclic arenyl group, a heterocyclic arenyl group or theophylline; and

Y is optionally substituted with at least one substituent, the or each substituent being chosen from linear or branched C_1-C_{20} alkyl optionally substituted with one or more carbocyclic or heterocyclic groups, or a substituent defined herein up to C_{20} cycloalkyl optionally including one or more heteroatoms from O, N and S, up to C_{20} bicycloalkyl optionally including one or more heteroatoms from O, N and S, up to C_{20} polycycloalkyl optionally including one or more heteroatoms from O, N and S, linear or branched C_1-C_{10} haloalkyl, linear or branched C_1-C_{10} perhaloalkyl, linear or branched C_2-C10 perhaloalkenyl, linear or branched C_2-C_{10} alkenyl, linear or branched C_2-C_{10} alkynyl, linear or branched C_1-C_{10} alkoxy, linear or branched C_1-C_{10} alkylthio, linear or branched C_1-C_{10} alkoxy (linear or branched C_1-C_{10} alkyl), linear or branched C_1-C_{20} alkoxycarbonyl, linear or branched C_1-C_{10} hydroxyalkyl, linear or branched aminoalkyl, aryl, substituted aryl, naphthyl, substituted naphthyl phenyl, heteroaryl, halogen, nitrile, nitro, amino, linear or branched C_1-C_{10} alkyl amino, linear or branched C_1-C_{10} dialkyl amino linear or branched C_1-C_{20}

alkoxycarbonyl, hydroxyl, formyl acetyl, carboxyl, carbonyl, amido, C_1-C_5 alkyl amido C_1-C_5 dialkylamido, aroyl, benzoyl, arylamino, diarylamino, aryl C_1-C_{10} alkyl amino, aziridino, pyrrolidino, piperidino, morpholino, thiomorpholino, indolino, piperazino, C_1-C_5 N-alkyl piperazino or N-aryl piperazino; and each cyclic substituent can in turn be substituted by one or more substituents as defined herein characterised in that the only bond rotation in the X linker is provided by an ethylene radical.

2. A compound according to claim 1, wherein X is a C_2-C_{10} aliphatic linker, preferably ethylene or carboxyethylene radical.

3. A compound according to claim 1 or 2, wherein Y is aziridino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, C_1-C_5 N-alkyl piperazino or N-aryl piperazino, pyrrolino, pyridino quinolino, pyrimidino, purino, pyrazino, pyrazolino, pteridino, pyridazino or pyridopyrimidinono, or an optionally substituted version thereof.

4. A compound according to claim 1, 2 or 3, wherein the Y group is substituted with a group including an aryl or substituted aryl group.

5. 1-(4-chlorobenzhydryl)-4-ethyl[2'[4"-(2-hydroxy-benzhydryl]piper idine]piperazine.

6. 1-4-chlorobenzhydryl)-4-ethyl-"[2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one]piperazine.

7. (4-chlorobenzhydryl-4-ethyl-[2'[4"-p-chlorophenyl)-4"-hydryoxy]piperidine]piperazine.

8. 1-(4-chlorobenzhydryl)-4-(3-phenyl-3-propanone)piperazine.

9. 1-(4-chlorobenzhydryl)-piperazine-4-ethyl-2'[4"(2,3,4-trimethoxybenzyl)piperazine.

10. A pharmaceutical composition comprising a compound according to any preceding claim and a pharmaceutically acceptable carrier.

11. A compound according to any of claims 1 to 9 for use as a medicament.

12. The use of a compound according to any preceding claim in the manufacture of a medicament for the treatment of an antihistamic condition.

13. The use of 4-chlorobenzhydryl piperazine ethyl chloride to make a compound according to any of claims 1 to 9.

14. The use of a 4-chlorobenzhydryl piperazine to make a compound according to any one of claims 1 to 9.

15. An antihistamine compound substantially as described herein with reference to the accompanying Examples.

16. The use of 4-chlorobenzhydryl piperazine ethyl chloride or 4-chlorobenzhydrylpiperazine substantially as described herein with reference to examples 1 to 7.

17. A pharmaceutical composition for oral administration substantially as described herein with reference to Example 9.

INTERNATIONAL SEARCH REPORT

International Application No
.../GB 01/01748

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/10 C07D295/08 C07D211/22 C07D471/04 C07D211/52
C07D473/08 A61K31/495 A61K31/551 A61P37/08
//(C07D471/04,239:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

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Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2001	20/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Zervas, B

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